

CLAIMS:

1. The use of NIK or a mutein, variant, fusion protein, functional derivative, circularly
5 permutated derivative or fragment thereof for modulating the interaction between IL-2
common gamma chain (c γ c) and NIK.
2. The use according to claim 1, wherein the fragment of NIK comprises the C-terminus
of NIK (from residue 624 to 947, SEQ ID NO:19).
3. The use according to claim 1, wherein the fragment of NIK comprises NIK 640-720
(SEQID NO: 18).
- 10 4. The use according to claim 1, wherein the mutant of NIK is AlyNIK.
5. The use of a DNA encoding NIK or a mutein, variant, fusion protein, circularly
permutated derivative or fragment thereof for modulating the interaction between IL-2
common gamma chain (c γ c) and NIK.
6. The use of an antibody specific to NIK or to a mutein, variant, fusion protein,
15 functional derivative, circularly permutated derivative or fragment thereof for
modulating the interaction between IL-2 common gamma chain (c γ c) and NIK.
7. The use of a small molecule capable of modulating the interaction between IL-2
common gamma chain (c γ c) and NIK for modulating signalling trough c γ c, wherein
said molecule is obtainable by screening products of combinatorial chemistry in a
20 luciferase system.
8. The use of a DNA encoding the antisense of NIK or a mutein, variant, fusion protein,
circularly permutated derivative or fragment thereof for modulating the interaction
between IL-2 common gamma chain (c γ c) and NIK.
9. The use of NIK or a mutein, variant, fusion protein, functional derivative, circularly
25 permutated derivative or fragment thereof, in the manufacture of a medicament for the
treatment of a disease, wherein a cytokine stimulating signalling trough the IL-2 c γ c is
involved in the pathogenesis of the disease.

10. The use according to claim 9, wherein the cytokine is IL-12.
11. The use according to claim 9, wherein the cytokine is IL-15.
12. The use according to claim 9, wherein the fragment of NIK comprises the C-terminus of NIK (from residue 624 to 947, SEQ ID NO:19).
- 5 13. The use according to claim 9, wherein the fragment of NIK comprises NIK 640-720 (SEQID NO: 18).
14. The use according to claim 9, wherein the mutant of NIK is AlyNIK.
15. The use of NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, for inhibiting signalling trough IL-2 $\gamma\gamma$.
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16. The use of an antibody capable of recognize and binding NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, wherein a cytokine stimulating signalling trough the IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.
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17. The use of a DNA encoding NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.
- 20 18. The use of a DNA encoding the antisense of NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.
- 25 19. The use of a small molecule capable of modulating NIK- $\gamma\gamma$ interaction in the manufacture of a medicament for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.
20. A method for the treatment of a disease involving signalling of a cytokine trough IL-2 $\gamma\gamma$ in the pathogenesis of said disease comprising administration of a therapeutically

effective amount of NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in a subject in need.

21. The method according to claim 20, wherein the cytokine is IL-12.

22. The method according to claim 20, wherein the cytokine is IL-15.

5 23. The method according to claim 20, wherein the fragment of NIK comprises the C-terminus of NIK (from residue 624 to 947, SEQ ID NO:19).

24. The method according to claim 20, wherein the fragment of NIK comprises NIK 640-720 (SEQID NO: 18).

25. The method according to claim 20, wherein the mutant of NIK is AlyNIK.

10 26. A method for the treatment of a disease involving a cytokine stimulating signalling through $\gamma\gamma$ in the pathogenesis of said disease comprising the administration of a therapeutically effective amount of an antibody capable of recognizing and binding NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, to a subject in need

15 27. A method for the treatment of a disease involving a cytokine stimulating signalling through $\gamma\gamma$ in the pathogenesis of said disease comprising administration of a therapeutically effective amount of DNA encoding NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, to a subject in need.

20 28. A method of treatment of a disease involving a cytokine stimulating signalling through $\gamma\gamma$ in the pathogenesis of said disease comprising administration therapeutically effective amount of DNA encoding the antisense of NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, to a subject in need.

25 29. A method for treatment of a disease involving a cytokine able to stimulate $\gamma\gamma$ in the pathogenesis of said disease comprising administration of a therapeutically effective amount of a small molecule capable of modulating NIK- $\gamma\gamma$ interaction to a subject in need.

30. A pharmaceutical composition comprising NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ($\gamma\gamma$) and NIK.
- 5 31. A pharmaceutical composition comprising a DNA encoding NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ($\gamma\gamma$) and NIK.
- 10 32. A pharmaceutical composition comprising an antibody specific to NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ($\gamma\gamma$) and NIK.
- 15 33. A pharmaceutical composition comprising a small molecule capable of modulating the interaction between IL-2 common gamma chain ($\gamma\gamma$) and NIK, wherein the small molecule is obtainable by screening small molecules prepared by combinatorial chemistry in a luciferase system.
34. A pharmaceutical composition comprising a DNA encoding the antisense of NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for modulating the interaction between IL-2 common gamma chain ($\gamma\gamma$) and NIK.
- 20 35. A pharmaceutical composition comprising NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein a cytokine stimulating IL-2 $\gamma\gamma$ signalling is involved in the pathogenesis of the disease.
- 25 36. A pharmaceutical composition comprising NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein a cytokine stimulating signalling through IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.
37. A pharmaceutical composition comprising an antibody capable of recognizing and binding NIK or a mutein, variant, fusion protein, functional derivative, circularly

permuted derivative or fragment thereof, for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.

5 38. A pharmaceutical composition comprising a DNA encoding NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.

10 39. A pharmaceutical composition comprising a DNA encoding the antisense of NIK or a mutein, variant, fusion protein, circularly permuted derivative or fragment thereof, for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.

40. A pharmaceutical composition comprising a small molecule capable of modulating NIK- $\gamma\gamma$ interaction for the treatment of a disease, wherein a cytokine stimulating signalling trough IL-2 $\gamma\gamma$ is involved in the pathogenesis of the disease.

15 41. A pharmaceutical composition comprising a therapeutically effective amount of NIK or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof for treatment of a disease wherein NIK and $\gamma\gamma$ interaction is involved in the pathogenesis of the disease.

20 42. A polypeptide fragment of NIK, comprising the IL-2R common gamma chain ($\gamma\gamma$) binding domain, or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.

43. A polypeptide fragment of NIK according to claim 42, comprising the C-terminus of NIK (from residue 624 to 947, SEQ ID NO:19).

25 44. A polypeptide fragment of NIK according to claim 42, comprising NIK 640-720 (SEQID NO: 18).

45. A DNA encoding the polypeptide fragment of NIK according to anyone of claims 42 to 44.

46. A vector comprising the DNA according to claim 45.

47. A cell comprising a vector according to claim 46.
48. A method for the production of a NIK polypeptide fragment according to anyone of claims 42 to 44, comprising culturing a cell according to claim 47 and collecting the polypeptide produced.
- 5 49. An antibody, polyclonal or monoclonal, chimeric antibody, fully humanized antibody, anti-anti-Id antibody, intrabody or fragment thereof which specifically recognises and binds a polypeptide fragment of NIK according to anyone of claims 42 to 44.
50. A small molecule able to inhibit NIK- $\gamma\gamma$ interaction obtainable by screening of molecules prepared by combinatorial chemistry in a luciferase system.
- 10 51. A pharmaceutical composition comprising a polypeptide fragment of NIK according to anyone of claims 42 to 44.
52. A pharmaceutical composition comprising an antibody according to claim 49.
53. A pharmaceutical composition comprising a small molecule according to claim 50.
54. A pharmaceutical composition comprising a vector according to claim 47.
- 15 55. A pharmaceutical composition comprising a DNA according to claim 45.
56. The pharmaceutical composition according to anyone of claims 51 to 55, for modulating signalling through $\gamma\gamma$.
57. The pharmaceutical composition according to anyone of claims 42 to 44, for the treatment of a disease wherein NIK and $\gamma\gamma$ interaction is involved in the pathogenesis of said disease.
- 20 58. The use of a polypeptide fragment of NIK according to anyone of claims 42 to 44, in the manufacture of a medicament for treatment of a disease, wherein the activity of a cytokine having the common gamma chain in its receptor is involved in the pathogenesis of said disease.
- 25 59. The use according to claim 58, wherein IL-2 is involved in the pathogenesis of the disease.
60. The use according to claim 58, wherein IL-15 is involved in the pathogenesis of the disease.

- 5 61. The use of a fragment of NIK, comprising the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for treatment of a disease, disease wherein NIK and $\gamma\gamma$ interaction is involved in the pathogenesis of said disease.
62. The use of a fragment of NIK, comprising the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment and/or prevention of a disease resulting from excessive immune responses.
- 10 63. The use according to claim 62, for the treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis.
- 15 64. The use of a fragment of NIK, comprising the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof, in the manufacture of a medicament for the treatment and/or prevention of autoimmune diseases.
65. The use according to claim 64, wherein the disease is selected from immune thyroiditis, rheumatoid arthritis and other arthropaties, autoimmune haemolytic anemia and inflammatory bowel disease.
- 20 66. A method for the treatment and/or prevention of a disease in which activation of a cytokine, having the common gamma chain in its receptor, is involved in the pathogenesis of the disease, comprising administering a therapeutically effective amount of a polypeptide fragment of NIK, comprising the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof to a subject in need.
- 25 67. A method according to claim 66, wherein IL-2 is involved in the pathogenesis of the disease.
68. A method according to claim 66, wherein IL-15 is involved in the pathogenesis of the disease.

69. A method of treatment and/or prevention of a disease in which NIK and $\gamma\gamma$ interaction is involved in the pathogenesis of said disease, comprising administering to a host in need thereof a therapeutically effective amount of a polypeptide comprising a fragment of NIK, comprising the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.
70. A method of treatment and/or prevention of a disease in which NF- κ B activation is involved, comprising administering to a host in need thereof an effective amount of a fragment of NIK, corresponding to the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.
71. A method of treatment and/or prevention of a disease in which NF- κ B activation is involved, comprising administering to a host in need thereof an effective amount of a small molecule according to claim 50.
72. A method according to anyone of claims 69 or 70, for the treatment of cancer.
- A method according to anyone of claims 69 or 70, for the treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis.
73. A method of treatment and/or prevention of a disease resulting from excessive immune responses, comprising administering to a host in need thereof a therapeutically effective amount of a polypeptide comprising a fragment of NIK, corresponding to the $\gamma\gamma$ binding domain (SEQ ID NO: 18), or a mutein, variant, fusion protein, functional derivative, circularly permuted derivative or fragment thereof.
74. A method according to claim 73, for the treatment of rheumatoid arthritis, osteoarthritis, inflammatory bowel disease, asthma, cardiac infarct, Alzheimer's disease, or atherosclerosis.